Population Pharmacokinetics and Pharmacodynamics of Artemether and Lumefantrine during Combination Treatment with Uncomplicated Falciparum Malaria

EN.580.640 Systems Pharmacology and Personalized Medicine

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1. Introduction

For this project, we are looking at the effects of artemether (ARM) and lumefantrine (LUM) on acute *Plasmodium falciparum* malaria. Malaria is a "febrile illness caused by intracellular protozoa [... that is] transmitted by the bite of an infected female mosquito" [1]. Malaria is a leading cause of death worldwide. Every year, 2.2 billion people are exposed to the disease and ~300 million people will contract it. In 2006, 1 million deaths were caused by the disease, most of whom were children. Yet, treatment has recently been improving with only 438,000 malaria deaths in 2015. Malaria disproportionately affects poor regions of Africa, with 88% of all malaria cases occurring in sub-saharan Africa [2]. The prevalence of the disease contributes to the economic problems in these regions as "African countries spend US$12 billion annually on malaria, with individual African families spending up to 25% of their income on malaria prevention and control" [1]. A report from the World Health Organization estimated that from 1965 to 2000, the GDP of African countries grew at a 32% slower rate then they would have in the absence of malaria [3].

A recent issue with antimalarial drugs has been increased resistance. Chloroquine and sulfadoxine–pyrimethamine have both shown rapidly increasing resistance rates across sub-saharan Africa. That is why many countries have begun to switch to artemisinin-based combination therapy (ACT) [2]. The combination we will be looking at is artemether and lumefantrine. Artemether will act rapidly when the drug is taken and has a half-life of 1 to 3 hours. Artemether kills the parasite because it "interferes with parasite transport proteins, disrupts parasite mitochondrial function, inhibits angiogenesis and modulates host immune function" [1]. Also, artemether is cleared by metabolism into dihydroartemisinin (DHA). Both forms of the drug are active [4]. On the other hand, lumefantrine is a very slow acting drug. It has a half-life of 3-6 days, staying in the body for much longer periods of time. Lumefantrine works because it interferes with the parasite's ability to transform heme into hemozoin. Heme is created by the parasite during the breakdown of hemoglobin, but the compound is toxic to the parasite. The parasite has a mechanism to transform the heme into a non-toxic form: hemozoin. By blocking this process, lumefantrine increases toxic heme level high in the blood, killing remaining parasites left over after the artemether is cleared from the system. The two drugs work in unison to rapidly clear as much parasite as possible, and then to kill any lingering parasite.

2. Model Description

Three models are designed in this project, which are LUM Drug Model, ARM/DHA Drug Model and Parasite Model. The drugs are administered at 0, 8, 24, 36, 48,and 60 hours. Total time is 72 hours, 3 days. Each tablet contains 20 mg artemether and 120 lumefantrine. Dosing is based on patient weights as in Table 1.

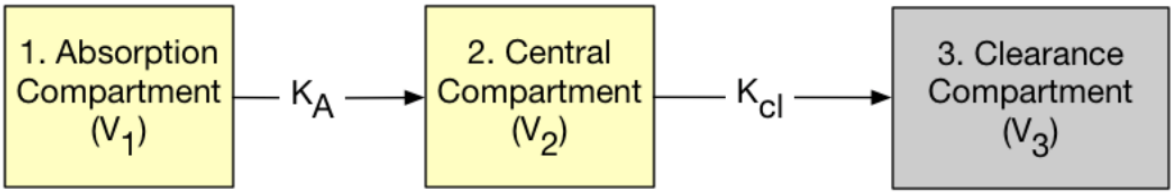
Weights (kg)	Tablet
5-14	1
14-24	2
24-34	3
>34	4

Table 1 Weight-based Dosing

The parasite model was set up to only looks at short term, so the LUM drugs will have no effect on the parasite model. However, it is still important to track LUM concentration as it is still a necessary component for the combination drug to be effective in a long term, even if our short term model doesn't reflect this.

2.1 LUM Drugs Model

The LUM Drugs Model[4] in Figure 1 has three compartments, two are virtual compartments for dose absorption (compartment 1) and dose clearance (compartment 3), and one is the central compartment, which represents [LUM]. We created virtual compartment volumes (V_1 and V_3) to be 1 L.

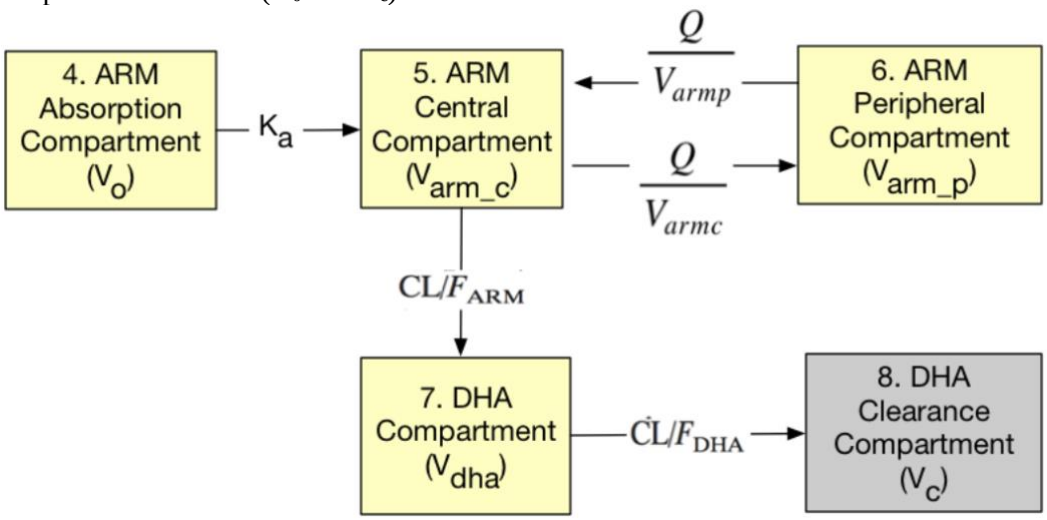


$$dydt(1) = -K_A * y(1)$$
$$dydt(2) = \frac{V_1}{V_2} * K_A * y(1) - y(2) * \frac{K_{cl}}{V_2}$$
$$dydt(3) = -y(2) * \frac{K_{cl}}{V_2} * \frac{V_2}{V_3}$$

Figure 1 LUM Drugs Model [4]

2.2 ARM/DHA Drugs Model

The LUM Drugs Model [4] in Figure 2 has five compartments, two are virtual compartments for dose absorption (compartment 4) and dose clearance (compartment 8), one is the central compartment for ARM, one is the peripheral compartment for ARM, and one is the compartment for DHA. We created virtual compartment volumes (V_0 and V_c) to be 1 L.



$$dydt(4) = -K_a * y(4)$$

$$dydt(5) = -y(4) * K_a * \frac{V_o}{V_{armc}} - \frac{Q}{V_{armc}} * y(5) - \frac{CL/F_{ARM}}{V_{armc}} * y(5) + y(6) * \frac{Q}{V_{armp}} * \frac{V_{armp}}{V_{armc}}$$

$$dydt(6) = y(5) * \frac{Q}{V_{armc}} * \frac{V_{armc}}{V_{armp}} - y(6) * \frac{Q}{V_{armp}}$$

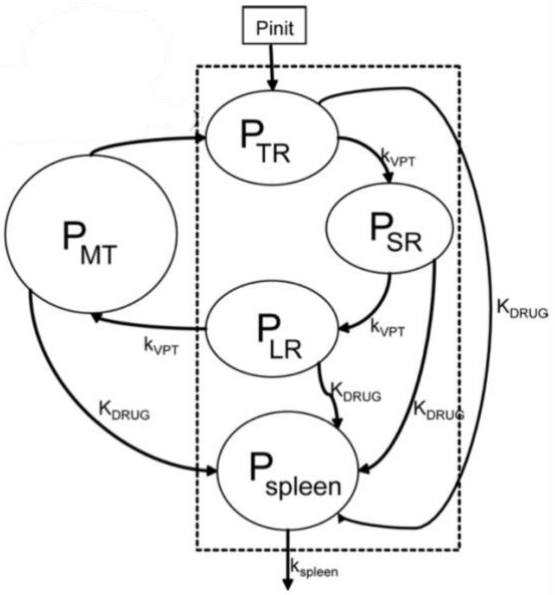
$$dydt(7) = y(5) * \frac{CL/F_{ARM}}{V_{armc}} * \frac{V_{armc}}{V_{dha}} - y(7) * \frac{CL/F_{DHA}}{V_{dha}}$$

$$dydt(8) = y(7) * \frac{CL/F_{DHA}}{V_{dha}} * \frac{V_{dha}}{V_c}$$

Figure 2 ARM/DHA Drugs Model [4]

2.3 Parasite Model

The Parasite Model [4] in Figure 3 has five compartments, which are tiny ring (P_{TR}), small ring (P_{SR}), large ring (P_{LR}), mature trophozoites/schizonts (P_{MT}), and P_{spleen}. The initial amounts of each of the 4 stages of parasite were taken by running the model for 4 complete loops of the intraerythrocytic cycle, the mean time of which is MTT in the parameters. The model is set up to contain a sin component which represents the natural fluctuations of parasite within the blood. We decided to not use this part of the model for two reasons. Firstly, the fluctuations would be fairly imperceptible when looking at the concentration of parasite that we start our model with. Secondly, these fluctuations are ultimately uninteresting, as we are more interested in seeing how far the concentration of the parasites will drop, and at these small levels, the fluctuation in the model will add noise that can misrepresent data.



$$\frac{dP_{\mathrm{TR}}}{dt} = P_{\mathrm{init}} + k_{\mathrm{IPT}} \times P_{\mathrm{MT}} \times \mathrm{REPL} \times \left(1 + \mathrm{A} \times \mathrm{SIN}\left(\frac{2\Pi}{\mathrm{MTT}} \times t\right)\right) - P_{\mathrm{TR}}\left(k_{\mathrm{VPT}} + k_{\mathrm{ARM}} + k_{\mathrm{DHA}}\right) \quad (1)$$

$$\frac{dP_{\mathrm{SR}}}{dt} = k_{\mathrm{VPT}} \times P_{\mathrm{TR}} - P_{\mathrm{SR}}\left(k_{\mathrm{VPT}} + k_{\mathrm{ARM}} + k_{\mathrm{DHA}}\right) \quad (2)$$

$$\frac{dP_{\mathrm{LR}}}{dt} = k_{\mathrm{VPT}} \times P_{\mathrm{SR}} - P_{\mathrm{LR}}\left(k_{\mathrm{VPT}} + k_{\mathrm{ARM}} + k_{\mathrm{DHA}}\right) \quad (3)$$

$$\frac{dP_{\mathrm{MT}}}{dt} = k_{\mathrm{VPT}} \times P_{\mathrm{LR}} - P_{\mathrm{MT}}\left(k_{\mathrm{IPT}} \times \left(1 + \mathrm{A} \times \mathrm{SIN}\left(\frac{2\Pi}{\mathrm{MTT}} \times t\right)\right) + k_{\mathrm{ARM}} + k_{\mathrm{DHA}}\right) \quad (4)$$

$$\frac{dP_{\mathrm{spleen}}}{dt} = k_{\mathrm{ARM}}\left(P_{\mathrm{TR}} + P_{\mathrm{SR}} + P_{\mathrm{LR}} + P_{\mathrm{MT}}\right) + k_{\mathrm{DHA}}\left(P_{\mathrm{TR}} + P_{\mathrm{SR}} + P_{\mathrm{LR}} + P_{\mathrm{MT}}\right) - k_{\mathrm{spleen}} \times P_{\mathrm{spleen}} \quad (5)$$

Figure 3 Parasite Model [4]

All the parameters are shown in Table 2 [4].

Type	Parameter	Value
ARM & DHA	k_a(per h)	1
	CL/F_{ARM}(liters/h/kg)	θ_1*[1+θ_2*(occ-1)], where $\theta_1 = 2.6$ and $\theta_2 = 0.57$
	V_{arm_c}(liter/kg)	5.2
	Q (liter/kg)	1.4
	V_{arm_p}liter/kg)	41.4
	CL/F_{DHA}(liters/h/kg)	6.8
	V_{dha_c}(liter/kg)	3.7
	K_A(per h)	0.82
	K_{cl} (ml/h/kg)	77
LUM	V_2 (liters/kg)	8.9
	P_{init}(parasites/μl)	1
	VPT (h)	15.5
Parasite	MTT (h)	48.5
	$REPL_p$	4
	A_p	0
	k_{spleen}	0.26
	k_{IPT}	1/(MTT-VPT)
	k_{VPT}	3/(VPT)
	k_{ARM}	$S_{ARM/DHA}$*log[ARM]
	k_{DNA}	$S_{ARM/DHA}$*log[DHA]
	$S_{ARM/DHA}$	0.073

Table 2 Parameters Setting [4]

3. Method of Analysis

3.1 Concentration and Sensitivity Analysis

Using the ordinary differential equations we built for the different compartments, we can describe the concentration changes of the drug over time in specific compartments. We plotted the drug response of the central compartment in the LUM model, that of the ARM central and peripheral compartments, and that of the DHA central compartment in the ARM/DHA model. By adding all the different compartments' drug concentrations in each model together, we are able to track the mole balance of the drug.

We performed a sensitivity analysis on our model. We increased each parameter in our model by 5%, and looked at the change in AUC for the LUM, ARM, and DHA concentration, as well as the C_{trough} for the parasite model. The responses were normalized in order to compare them.

3.2 Population Variability

Our LUM, ARM/DHA and Parasite models combined have a total of 22 parameters, some of which have effect on all three models, some of which have effect on two models (ARM & DHA model and Parasite model), and some of which just only have effect on one model (LUM model). For the population variability study, we choose three parameters: weight distribution, volume of LUM distribution, and central volume of ARM distribution.These distributions follow a normal distribution as shown in Table 3.We track four outputs: AUC and C_{trough} of LUM Drugs, AUC and C_{trough} of ARM drugs, AUC and C_{trough} of DHA drugs and log scale of C_{trough} of the Parasite.

Parameters	Numbers	Description
Weight Distribution (kg)	100	Mean = 43.91, SD = 11.55
Volume of central LUM Distribution (liters)	100	Mean = 8.9, SD = 2.45
Volume of central ARM Distribution (liters)	100	Mean = 5.2, SD = 1.2

Table 3 Set up for Normal Distributions of parameters

3.3 Missed Dose Analysis

Missing a dose for a drug can often greatly affect the pharmacokinetics and pharmacodynamics of a drug. This can be especially true in the drug combination that we are looking at. Artemether and Lumefantrine are only taken 6 times, meaning a missed dose could have major effects of drug concentrations and parasite clearance. To analyse how a missed dose will affect our drug therapy, we will be running our model for a missed dose. We will look at 4 outputs: The AUC of LUM, ARM, DHA, and the C_{trough} of the log of parasite concentration. The reason we look at Ctrough on a log scale is to obtain a better understanding of how effective the treatment is. Even a small amount of drug will clear a vast amount of a parasites. We need to look at a log scale as even if more drug clears out only .1% more

parasite, that is very significant to how effective the treatment is, and can be devastating to the parasites ability to grow back.

We will be looking at the second dose, at hour 8, as the missed dose. We looked at this dose because the first two doses are the most important. The are closer together (8 hours apart), because the goal is drop parasite concentration as quickly as possible. This is done by moving up the second dose by 4 hours, unlike the final 4 doses which occur 12 hours apart. We will look at 7 different situations. The first two will be a properly taken dose, and then a completely missed dose. We will also look at 5 late doses where the dose is taken at 3.2, 6.4, 9.6, 12.8, and 16 hours after the original dose time. The last time would mean the second and third dose will be taken at the same time. Information of how the drug should be taken specifically says that if a dose is missed, it should be taken as soon as the missed dose is remembered, but a missed dose is better than taking two doses at the same time [5].

4. Result/Discussion

4.1.1 Concentration and Mole Balance

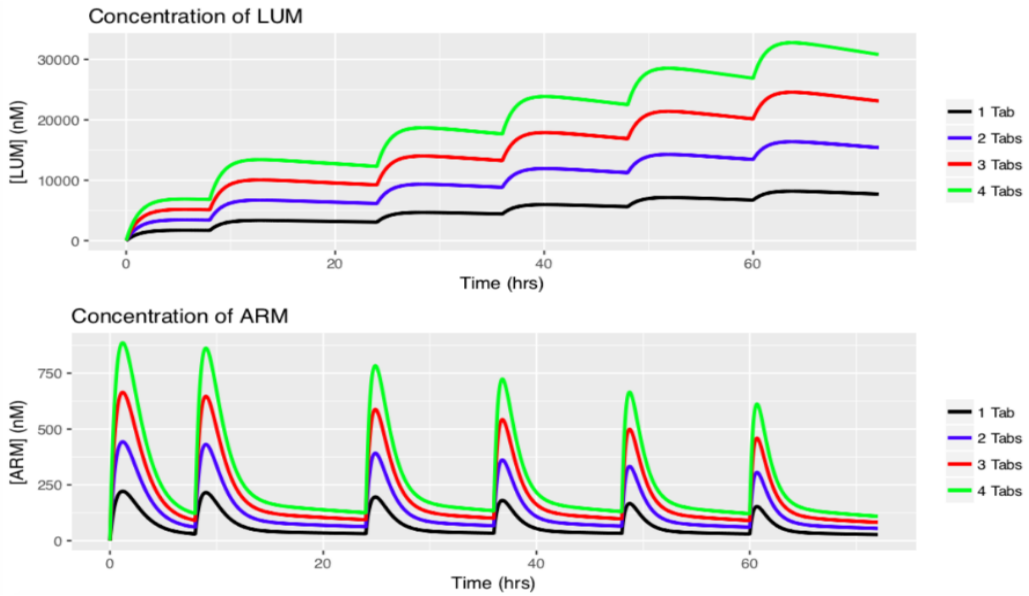


Figure 4. The LUM and ARM concentration response of a 43.91kg individual with metronomic dosings following different dosing regimens. Both figures are plotted with the Y-axis showing the drug concentration in the blood in unit of nanomoles and the X-axis showing time progression in unit of hours. The black, blue, red and green curves represents one-tablet, two-tablet, three-tablet, four-tablet consumption, respectively.

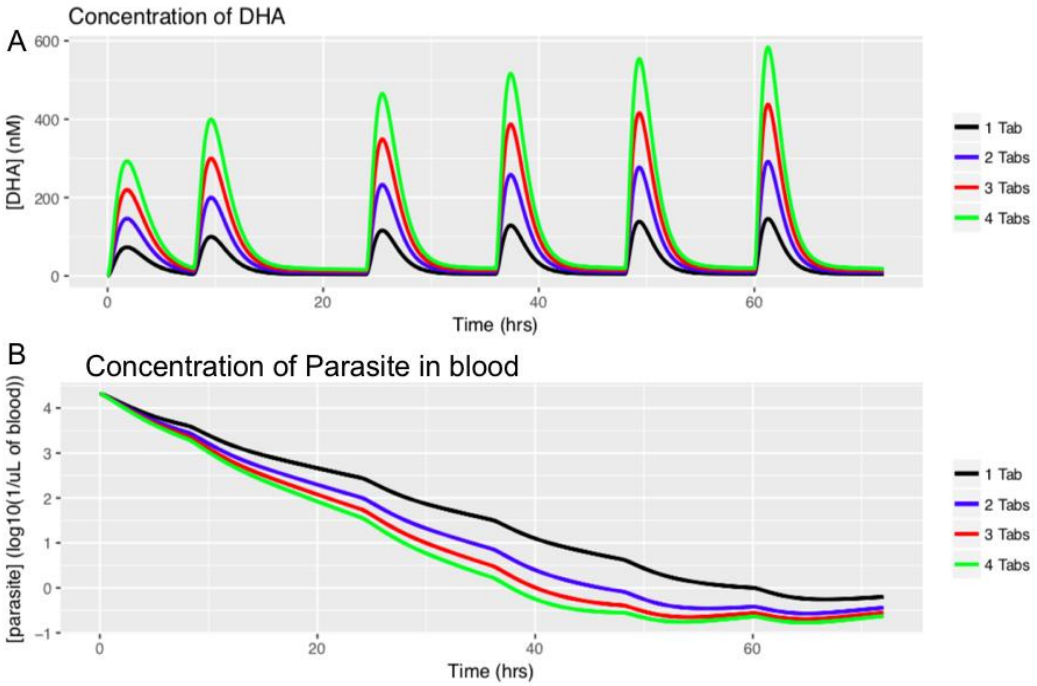


Figure 5A - the DHA concentration response of a 43.91kg individual with metronomic dosings following different dosing regimens. The Y-axis shows the drug concentration in the blood in unit of nanomoles and the X-axis showing time progression in unit of hours. ***Figure 5B*** - the concentration of parasite in blood of the same individual after intake of the drug cocktail(ARM and DHA). The Y-axis shows the common logarithm of parasite concentration in the blood in unit of 1/microliter of blood and the X-axis shows time progression in unit of hours. In both figures, the black, blue, red and green curves represent one-tablet, two-tablet, three-tablet, four-tablet drug intake, respectively.

The LUM concentration level(Figure 4) increases gradually over time reaching to a plateau, then enters into similar patterned cycle following additional new tablet intakes. This pattern exists because it takes longer time to absorb and excrete the LUM, elongating the drug's effective time in the body. The ARM concentration level(Figure 4) increases then decreases rapidly after consumption within the window of one drug intake. This means that the drug has a rapid onset of action in killing the parasite but at the same gets eliminated from the body quickly, making it necessary to intake additional dosage to maintain the ARM's drug efficacy. The peak concentration of the ARM within each intake window decreases after more ARM consumption. This decrease in the drug sensitivity effect is less prominent in the lower tablet dosing regimen. In both of the drugs, the more tablets consumed, the higher the drug concentrations are in the body. Similarly to ARM, its primary active metabolite DHA(Figure 5A) concentration level increases then decreases rapidly after consumption within the window of one drug intake. Compared with ARM, the DHA gets excreted from the body more rapidly. Unlike ARM, the peak concentration of DHA increases as the frequency of drug intake increases, meaning that the sensitivity of drug increases with more drug intake. The parasite concentration(Figure 5B) follows an exponential decay over time because the linear curve representing parasite concentration in the blood is in the scale of common logarithm. The more tablets per dose, the less parasite remains in the body.

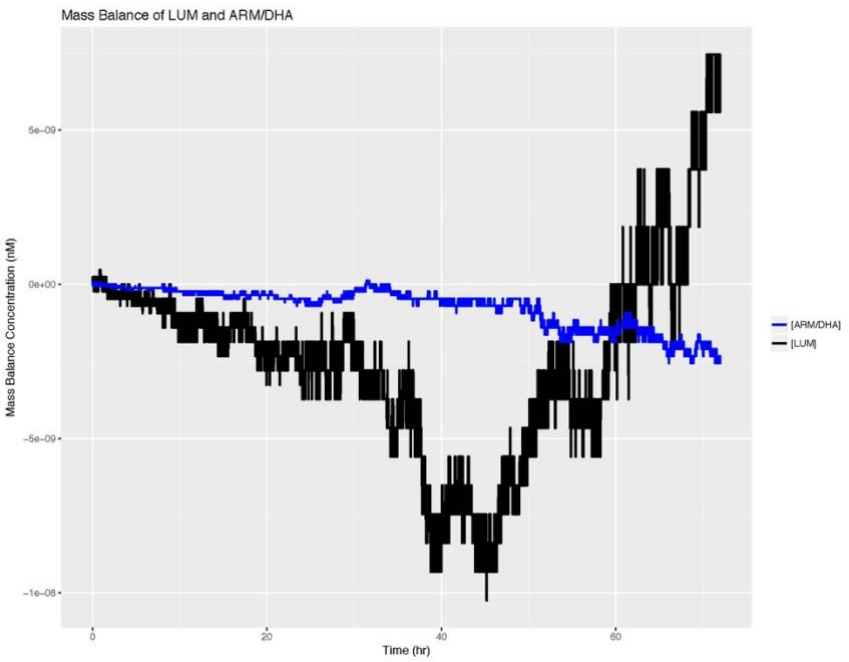


Figure 6 The mole balance of LUM and the mole balance of ARM/DHA

4.1.2 Sensitivity Analysis Results

Figure 7 Sensitivity Analysis of the combined models. The upper graph shows the sensitivity heatmap of LUM. The middle graph shows the sensitivity heatmap of ARM/DHA. The bottom graph shows the sensitivity heatmap of parasite.

We break down the sensitivity analysis into three parts, each representing one model's sensitivity of their model parameters. Green represents a favorable response and red represents the a negative response. Not all parameters are shown in each model, as some have no effect on that specific part of the model. In the LUM model, increasing mass has the most negative response to AUC while increasing tablet has the most positive response. This logically follows because as mass increases, the volume of the LUM compartment increases, and drug concentration will decrease. Inversely, if we increase the tablet (drug dose), more drug will be in the system, and concentration will increase. The increase and decrease are 1 to 1. In the ARM/DHA model, both drug AUCs are positively influenced by increasing tablet. The AUC of DHA is strongly influenced by the mass, while that of the ARM is only mildly influenced by mass. The volume of distribution has little influence over the AUCs of the two drugs. The C_{trough} of the parasite growth is strongly decreased by s, which determines how effective the drugs are. The VPT (visible compartment transfer rate) also mildly decreases C_{trough} because the longer the transition time for the parasite to grow to the next level, the slower the parasite will be able to grow back.

4.2 Population Variability Results

As is shown in Figure 8, weight influences the AUC of all three drugs. Central volume of LUM just influences the AUC of LUM. Central volume of ARM has little influence on the AUC of ARM and the AUC of DHA.

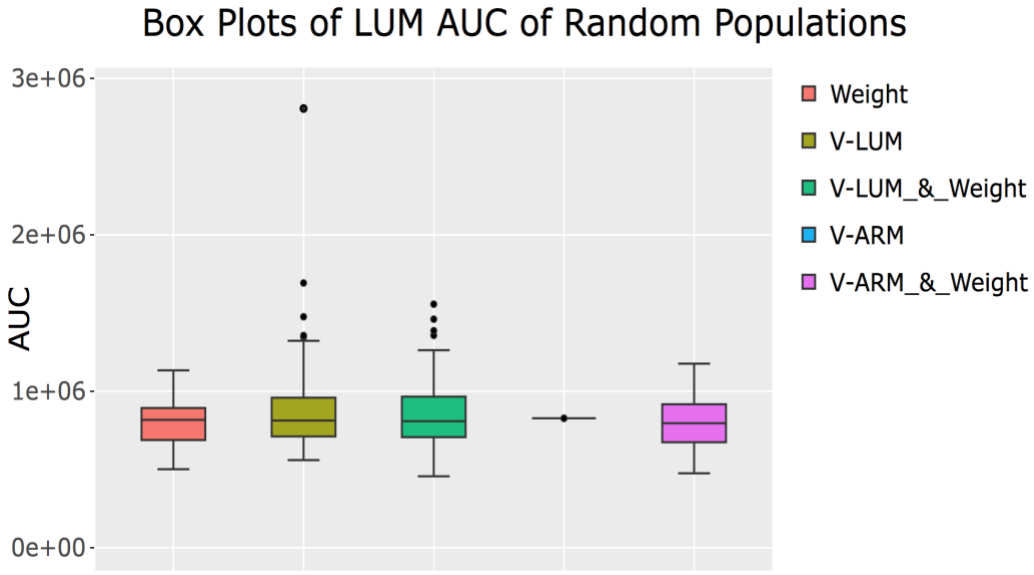


Figure 8-a Boxplot for LUM AUC

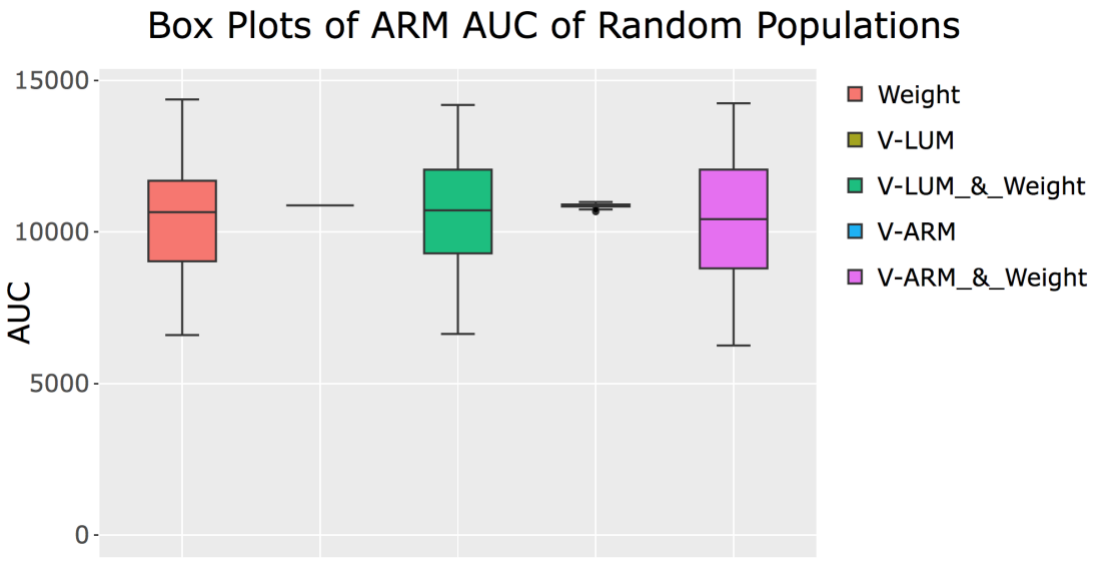


Figure 8-b Boxplot for ARM AUC

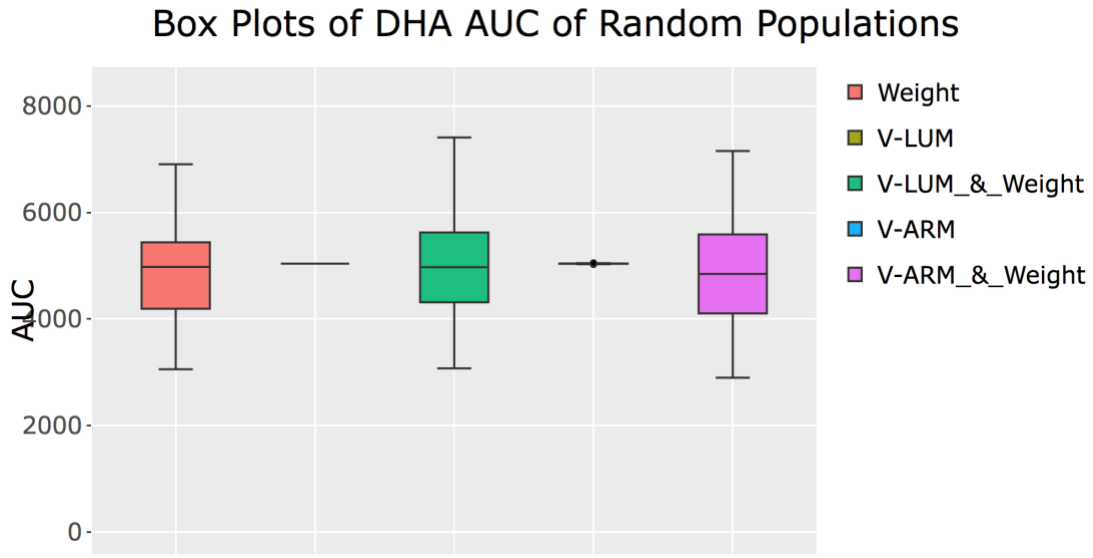


Figure 8-c Boxplot for DHA AUC

As is shown in Figure 9, weight influences all the three drugs C_{trough}. Central volume of LUM only influences the LUM C_{trough}. Central volume of ARM has little influence on the ARM drug AUC and DHA drug C_{trough}.

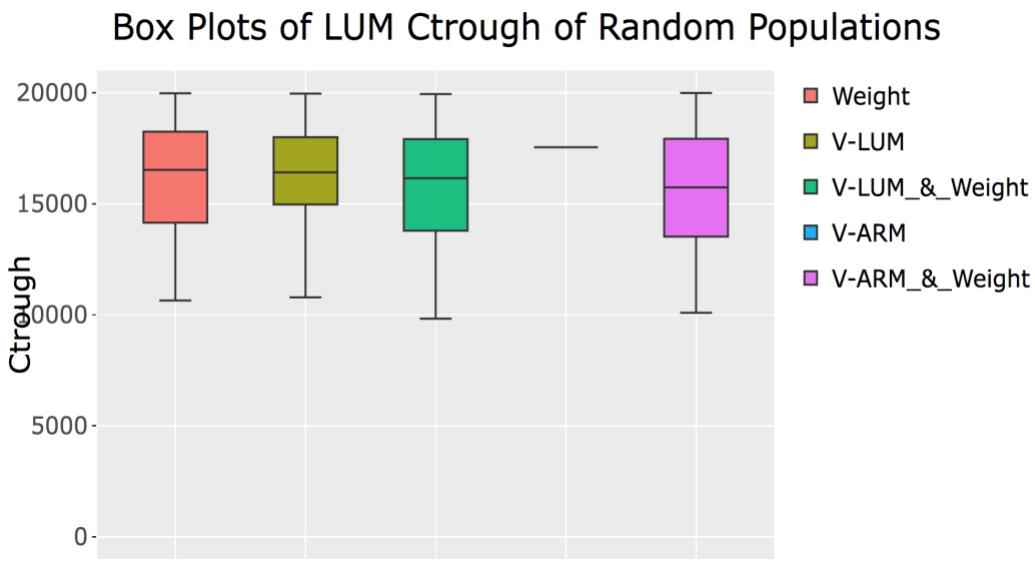


Figure 9-a Boxplot for LUM C_{trough}

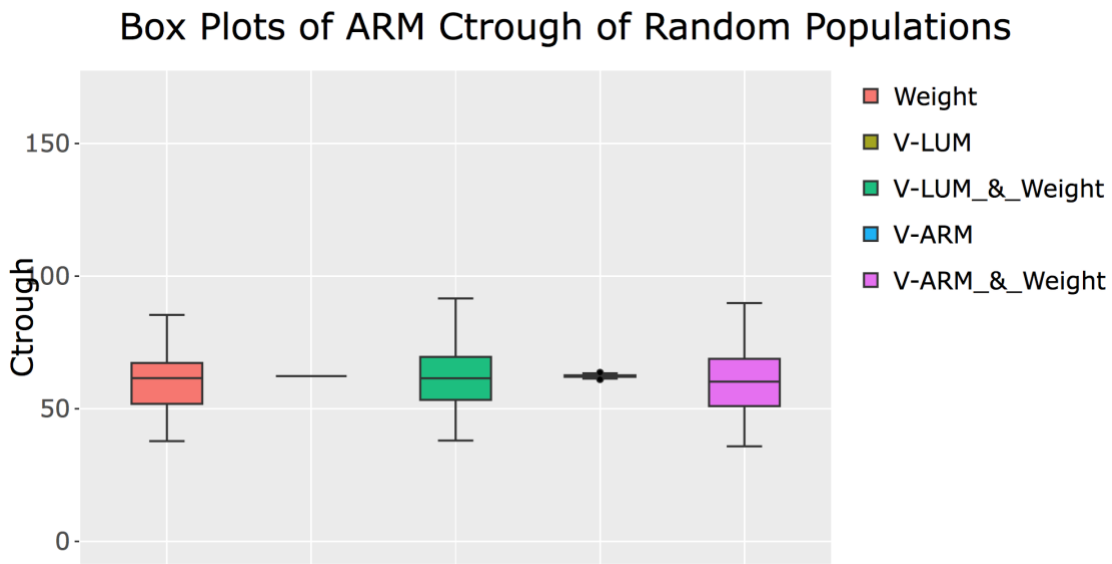


Figure 9-b Boxplot for ARM C_{trough}

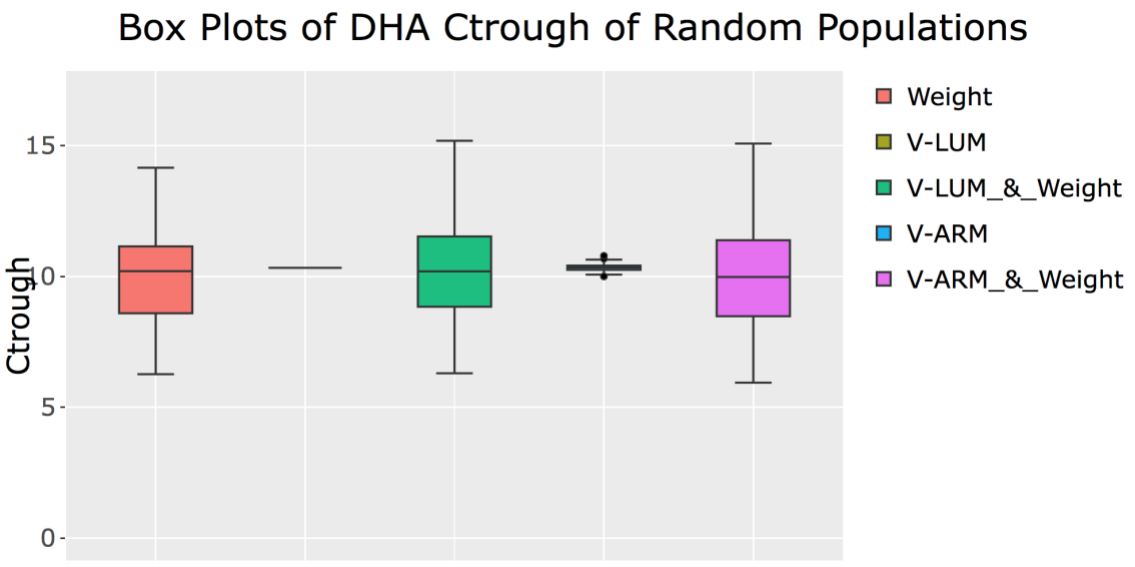


Figure 9-c Boxplot for DHA C_{trough}

As is shown in Figure 10, weight influences the Parasite C_{trough}. Central volume of LUM has no influence on the Parasite C_{trough}. Central volume of ARM has little influence on the Parasite C_{trough}.

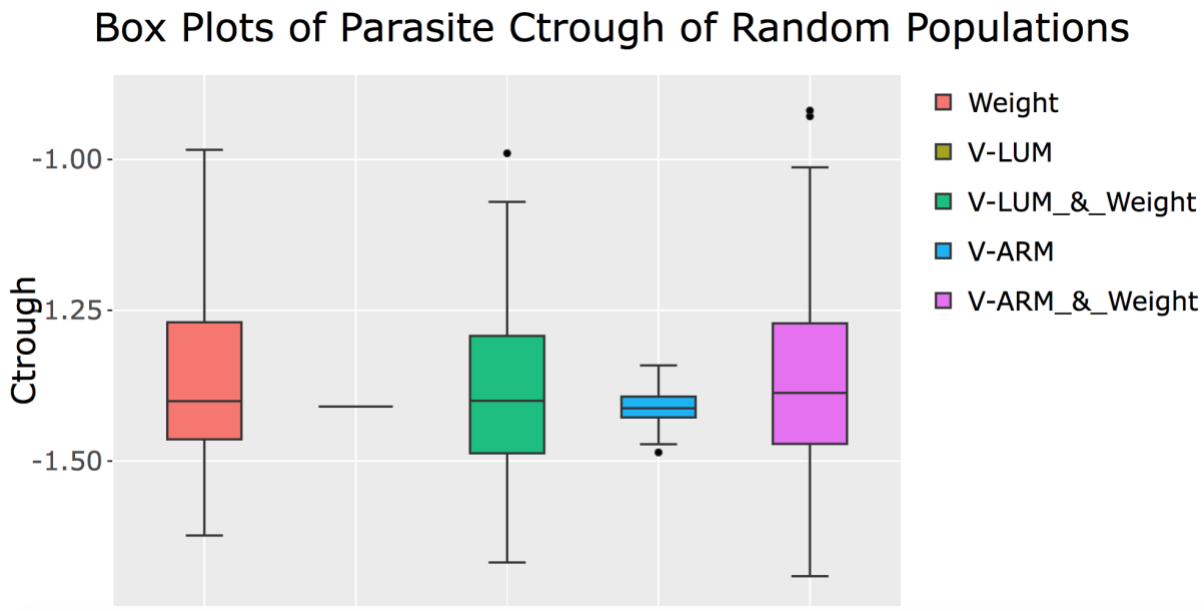


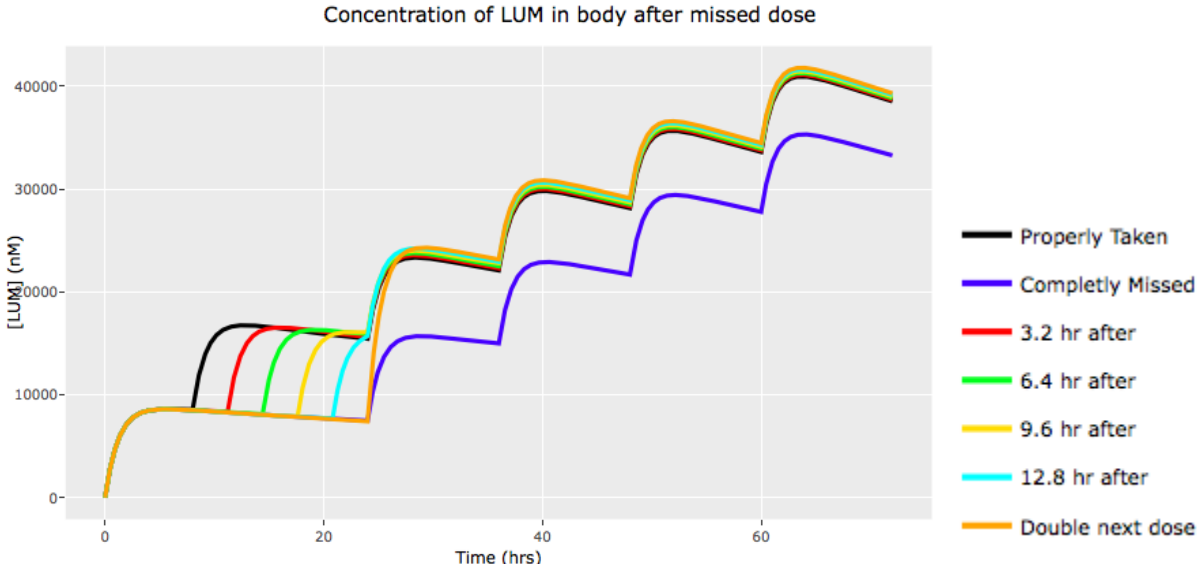
Figure 10 Boxplot for Parasite C_{trough}

These results match the sensitivity analysis perfectly. As is shown in the sensitivity analysis, weight has positive sensitivity to the parasite C_{trough} and negative sensitivity to the AUC of three drugs. Central volume of LUM just has negative sensitivity to the LUM AUC. Central volume of ARM has little sensitivity to the DHA and ARM drugs. We believe weight tends to have a much larger effect on the AUC and C_{trough} values because weight has much wider reacting effects across the model. Only changing the volume of one compartment is insignificant comparatively.

4.3 Missed dose result

As discussed above, we ran the test for a 5 kg person and looked at the AUC of LUM, ARM, and DHA concentration, as well as C_{trough} of the parasite. The results for each of the 4 tests are as follows.

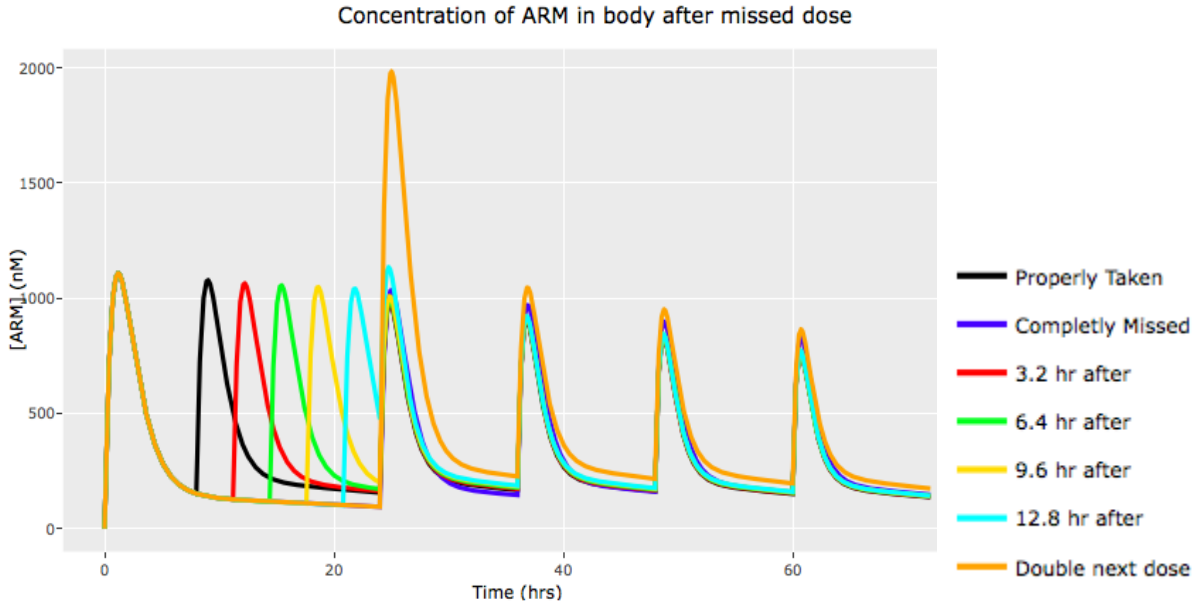
LUM- From looking at the AUC of the LUM, there is actually very little effect when a dose is taken later than it is supposed to be (figure 11). From proper dosing, to double taking on dose 3, the AUC is still 95.04% of its initial value. On top of this, if we look at the C_{trough} and C_{peak} for the drug during the time periods from dose 2 to dose 4, there is very little change between either measurement. If we look at a completely missed dose, we see a major drop in both C_{peak} and AUC. The AUC will drop to 75% of its proper dosage value. This outcome is sensible as LUM is absorbed into the body rapidly, while its half-life is very long (3-4 days). If you delay a dose, even by up to 16 hours, very little drug will have been cleared in that time, so AUC, C_{trough}, and C_{peak} will not be greatly affected. If you miss a dose, since so little drug is cleared, the missed doses will have long lasting effects. It is also important to note that we are only looking at this drug over the first 3 days, while the drug will typically stay in the body for a couple of weeks. These effects would most likely be more pronounced if we looked at them for longer periods.



AUC	Cpeak between 8 and 36 hr [nM]	Ctrough between 8 and 36 hr [nM]
1814917	23345	8510
1377169	15704	7421
1797881	23560	8289
1780367	23781	8064
1762362	24007	7844
1743851	24224	7630
1724820	24302	7421

Figure 11 LUM concentrations for missed dose analysis, followed by AUC, C_{peak}, and C_{trough} taken from the analysis

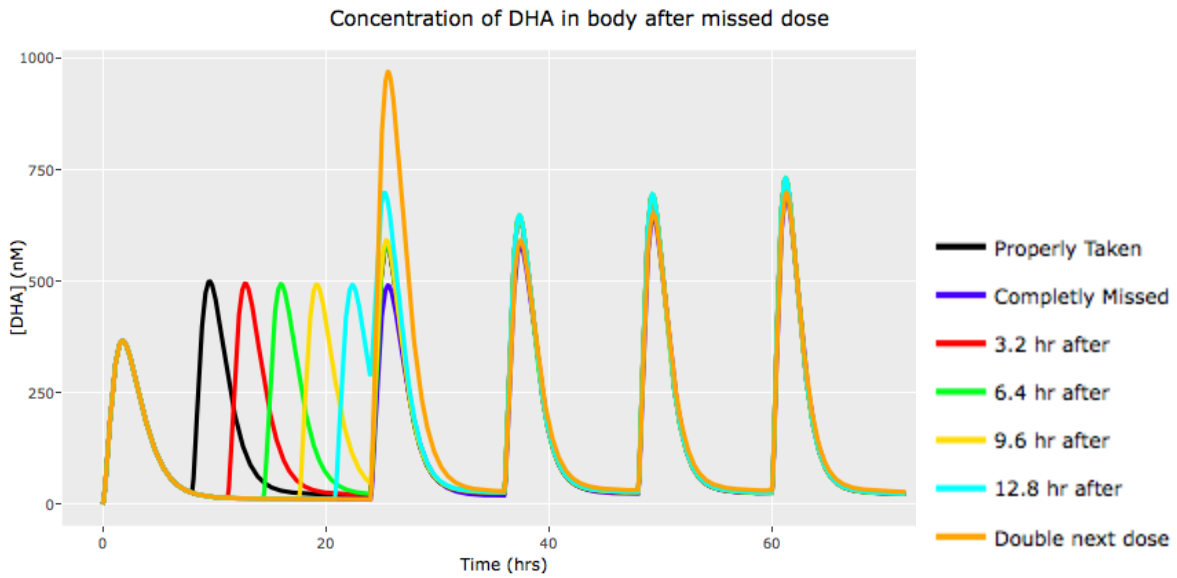
ARM- On the opposite end of the spectrum, we can look at ARM (figure 12). ARM clears from the body very quickly, so missing a dose only decreases the AUC to 89.46% the proper dosage AUC, much less than what was seen in the LUM case. Also, when looking at the delayed doses, we see very little change in C_{peak} or C_{trough}, as the drug from the previous dose has mostly cleared by the time the 3rd dose is given. When we look at the double dose, we actually see a really odd case. First, because most of the drug will clear before the next dose, double dosing greatly increases C_{peak}, 183.88% of the proper dose C_{peak}. This large increase is drug concentration is fairly alarming, and most likely the reason why the patient is discouraged from taking a double dose if a past dose is missed [5]. On top of this, the AUC actually increases to 110.7% of the proper dose AUC. This might seem like a good thing, but as we will see in the parasite model, the dose time is more important than the AUC of the drug. Overall, these results are consistent with the knowledge that AUC will be quickly absorbed and quickly cleared from the body.



AUC	Cpeak between 8 and 36 hr [nM]	Ctrough between 8 and 36 hr [nM]
23875	1079	152
21358	1036	95
23862	1065	127
23823	1056	117
23760	1049	109
23540	1134	102
26431	1983	95

Figure 12 ARM concentrations for missed dose analysis, followed by AUC, C_{peak}, and C_{trough} taken from the analysis

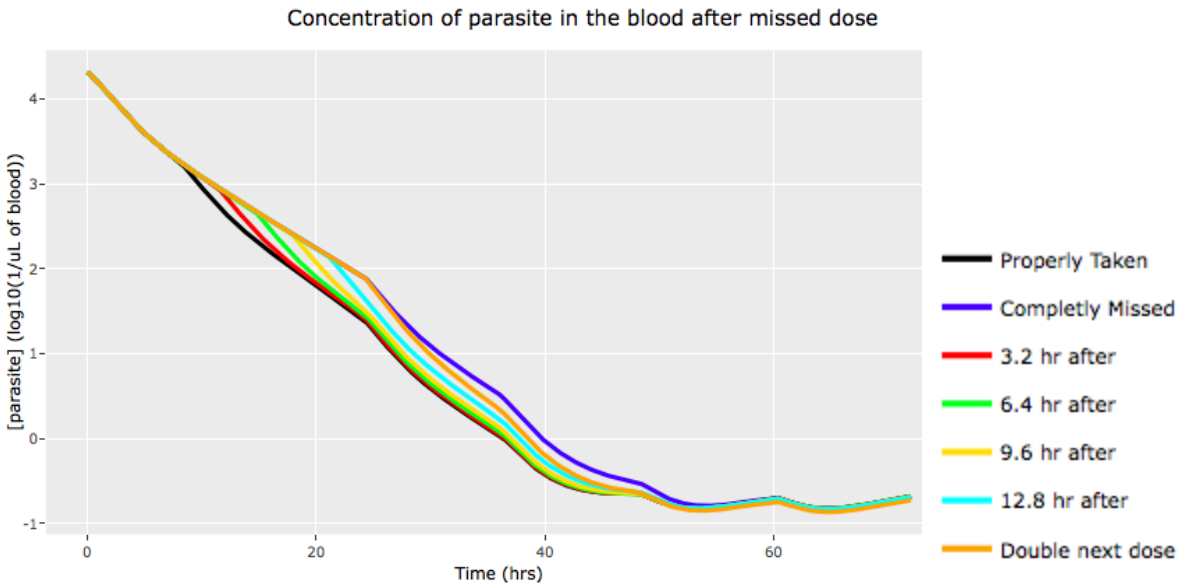
DHA- The DHA results are very similar to the results seen in ARM (figure 13). The main difference is that we do not see an increase in the AUC of the double dose, but the AUC is still 98.23% of the proper dose, so there is very little change in the AUC. We also see the jump in C_{peak} that was shown in ARM, but is much more gradual, the increase being more reflected in the delayed doses as they get closer to the double dose. This is due to the fact the DHA is the second part of the model. ARM clears by metabolizing into DHA, meaning DHA will inherently stay in the system for longer after the dose is given.



AUC	Cpeak between 8 and 36 hr [nM]	Ctrough between 8 and 36 hr [nM]
11064	581	19.7
9044	491	9.7
11055	582	13.9
11045	584	12.1
11035	592	11.2
11029	699	10.4
10869	970	9.7

Figure 13 DHA concentrations for missed dose analysis, followed by AUC, C_{peak}, and C_{trough} taken from the analysis

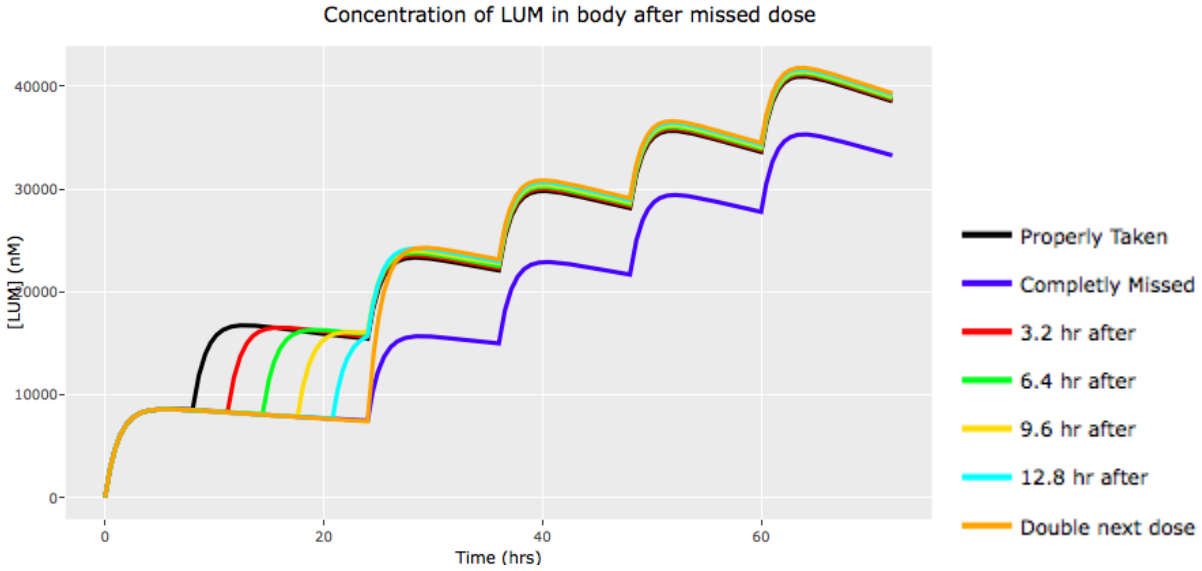
Parasite- For the parasite model, we looked at the C_{trough} of the log10 of parasite concentration. When we look at the C_{trough} for the entire 72 hours, we see that even if the dose is delayed or even missed, the C_{trough} is basically the same (figure 14). After the ARM has been administered, most of the parasite will eventually be cleared, leaving LUM to take care of what's left over. When we really start to see big changes in C_{trough} is when we look at how quickly the parasite is cleared out in the early stages. If we look at a missed dose, the C_{trough} rises from .1 to 1.2, a massive increase, and if the drug is double dosed, C_{trough} rises to .8. It is important to reiterate that the goal of taking the second dose at 8 hours to attempt to clear as much parasite as possible in the first day. Most patients who take the drug start to see major increases in wellness, as well as reductions in fever within one day of taking the drug. By missing or delaying this 8-hour dose, the drug is no longer having a quick of an effect as it is supposed, meaning the outcome is severely hindered. While double dosing might not decrease the AUC of ARM or DHA, it will have a major effect of how quickly the parasite is eliminated from the body.



Ctrough between 8 and 36 hr [log10(1/uL of blood)]	Ctrough [log10(1/uL of blood)]
0.10	-1.91
1.20	-1.93
0.13	-1.91
0.20	-1.92
0.30	-1.92
0.54	-1.93
0.80	-2.00

Figure 14 log10 of parasite concentrations for missed dose analysis, followed by C_{trough} taken from the analysis

Weight- We tested our model with weights between 5 to 50 kg, looking at intervals of 5 kg, and found that while changing the weight of a person can affect the specific concentration of drugs in the body, the overall patterns shown above are the same.



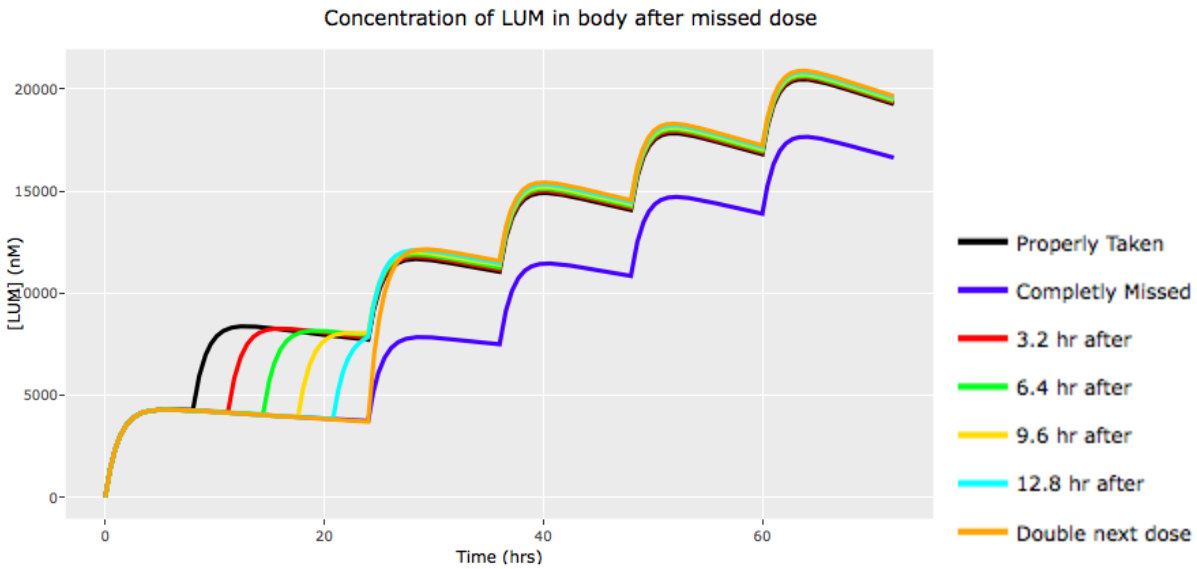


Figure 15 Top: LUM concentrations for missed dose analysis for 5kg individual; Bottom: LUM concentrations for missed dose analysis for 10kg individual

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